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CONVERSION OF SOME MONOCYCLIC β-LACTAMS INTO NOVEL DI-β-LACTAMS.

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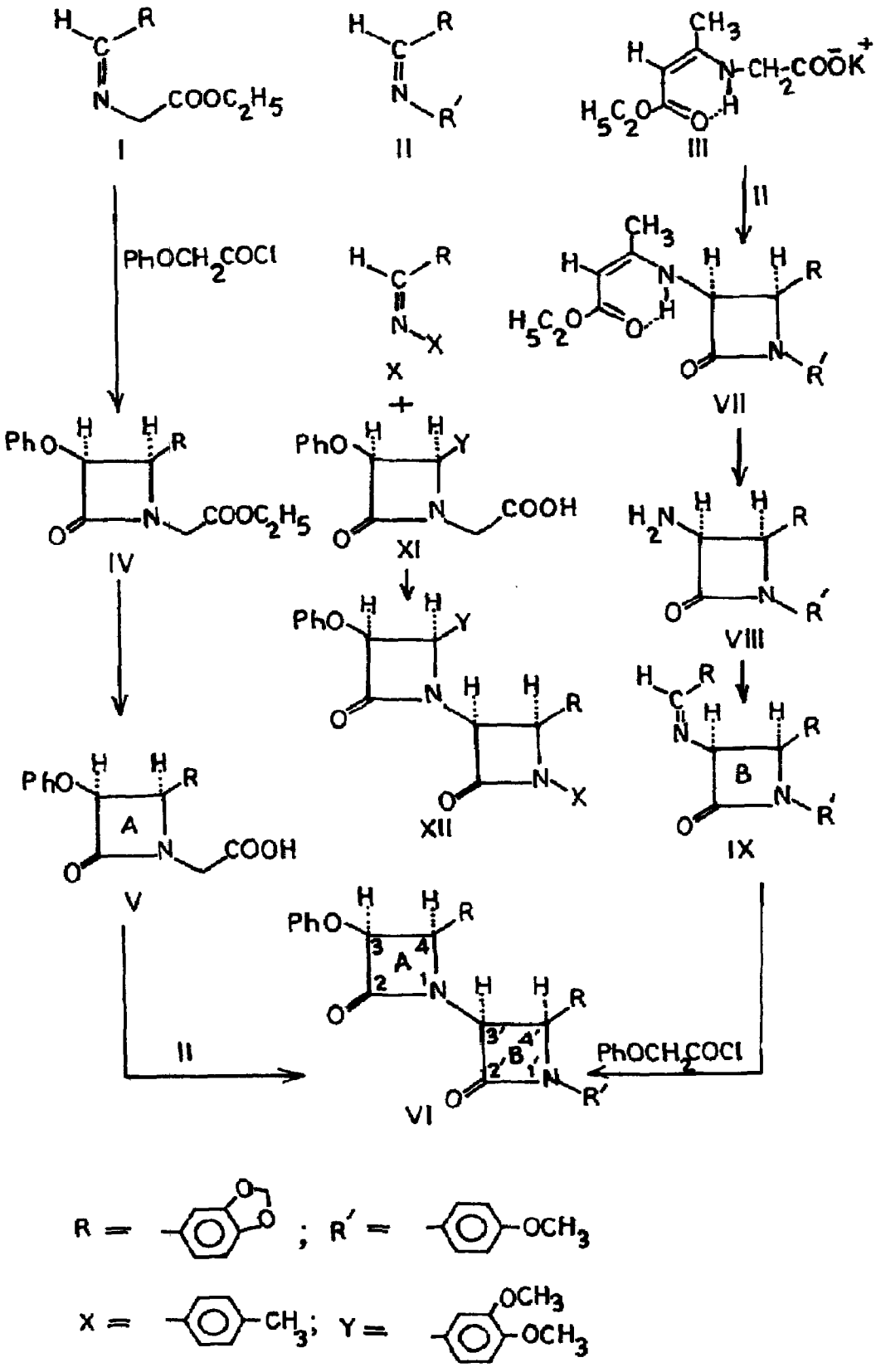
Abstract: Monocyclic β-lactams (V & XI) carrying a carboxy function have been used to annelate the Schiff bases (II & X) using $POCl_3$ in the presence of triethylamine to obtain the di-β-lactams (VI & XII). Alternately, (VI) could also be prepared by annelation of the Schiff base (IX) derived from the α-amino-β-lactam (VIII), with phenoxyacetyl chloride.

During the course of a project towards the synthesis of β-lactam antibiotics, we prepared several monocyclic β-lactams through the annelation of imines with suitable acid components using $POCl_3$ method.[1,2] The presence of free carboxy group is considered to be essential for antibacterial activity. To incorporate this function into monocyclic β-lactams, we discovered[3] an elegant use of glycine to prepare the Schiff base components such as (I). Reaction of (I) with phenoxyacetylchloride in the presence of triethylamine resulted in the β-lactam (IV) in high yield. Stereochemistry of this β-lactam was found to be cis from the value of coupling constant between C_3-H and C_4-H (J = 5.00 Hz). Saponification of a β-lactam ester usually leads to cleavage of β-lactam ring. However, (IV) could be easily converted to the acid β-lactam (V) under mild basic conditions[4] (0.1 N NaOH in acetone) without any harm to the β-lactam ring.

Besides antibacterial potential[5-7], monocyclic β-lactams have been converted to several fused ring β-lactams[8-10]. In the present communication, we wish to report the first example of the conversion of monocyclic-β-lactams (V & IX) into a novel di-β-lactam (VI) involving two different routes (see schemes). The crucial step in first approach is the use of the β-lactam (V) itself as an acid component to annelate the Schiff base (II) using $POCl_3$ method to prepare the di β-lactam (VI) in 55% yield, m.p. 245-46°C IR: 1755 cm^{-1} (β-lactam C=O).

The 90-MHz nmr spectrum (Fig. I) of the di β-lactam (VI) exhibited the β-lactam protons at δ 4.72 as a doublet (J = 5.5 Hz; 1H) and two closely placed doublets at 5.1 (J = 5.5 Hz; 3H). These values of the coupling constant reveal cis stereochemistry in both the β-lactam rings (A & B). To further confirm the stereochemistry, the di-β-lactam (VI) was alternatively prepared through the second approach in which the β-lactam ring (B) with a cis-stereochemistry was constructed first starting from glycine derivative[2] (III).


I
II
III
PhOCH2COCl
X
VII
IV
XI
VIII
V
XII
IX
VI
R = ; R′ = OCH3
X = CH3; Y = OCH3 OCH3

The compound (III) was condensed with Schiff base (II) using $POCl_3$ method to obtain the enamino-β-lactam (VII) which was then transformed to the α-amino-β-lactam (VIII) under mild acidic conditions. Stereochemistry of this β-lactam was found to be cis by its PMR spectrum in which C_3-H and C_4-H appeared as two doublets at δ4.61 and 5.2 with a coupling constant of 5.5 Hz. Moreover the high field appearance of $-NH_2$ protons at δ 1.5 also indicates the C_3-NH_2 group to be cis to the phenyl ring at C_4- and hence cis stereochemistry of the β-lactam (VIII). Reaction of (VIII) with piperonal in refluxing ethanol produced the aldimine (IX) in high yield. This α-imino-β-lactam (IX) was used as the Schiff base component which on annelation with phenoxyacetylchloride gave the desired di-β-lactam (VI).

To ascertain the reproducibility of the above technique, the di-β-lactam (XII) was prepared in high yield through the annelation of the Schiff base (X) with N-(2-oxoazetidino)acetic acid (XI). Further studies are being conducted for the synthesis of tri- and tetra-β-lactams from suitably constituted synthons in our laboratory. As can be easily visualised these compounds obtained from N-(2-oxoazetidino)acetic acids are analogous to peptides obtained from α-amino acids and hence shall be of academic as well as biological importance.

Elemental analysis on compounds IV-IX, XI and XII were in agreement with the structures.

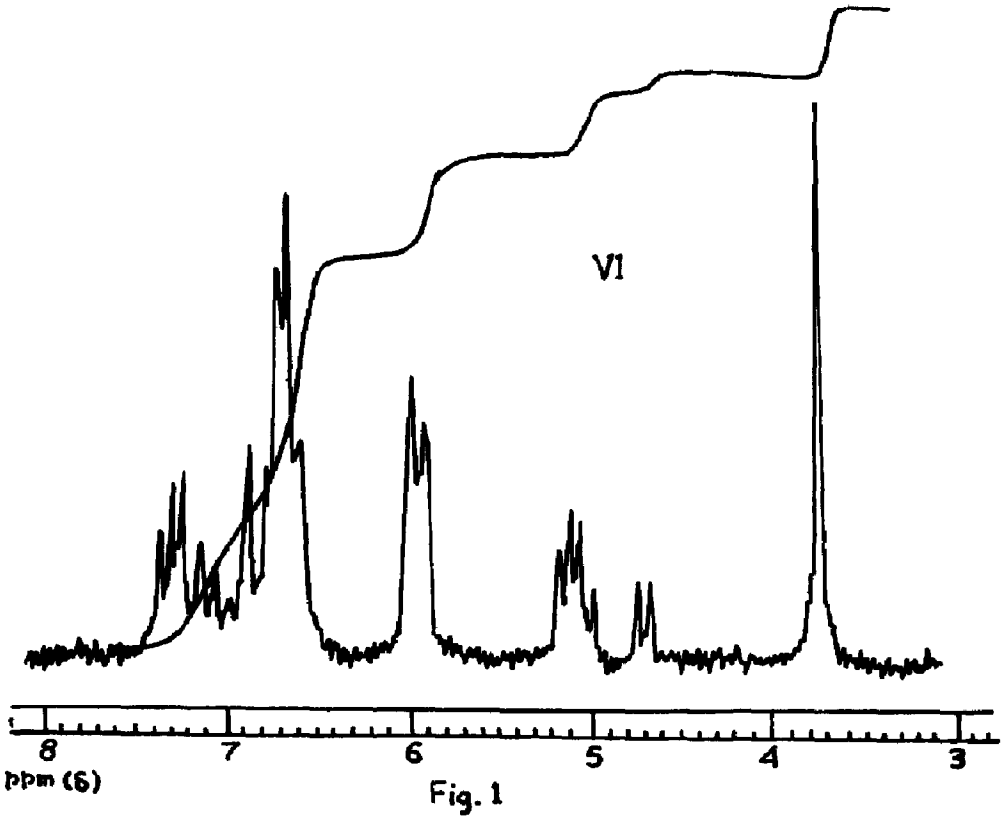


Fig. 1

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